SHORT REPORT

Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis

S Vulliemoz, F Lurati-Ruiz, F-X Borruat, J Delavelle, I J Koralnik, T Kuntzer, J Bogousslavsky, F Picard, T Landis, R A Du Pasquier

J Neurol Neurosurg Psychiatry 2006;**77**:1079–1082. doi: 10.1136/jnnp.2006.092353

Progressive multifocal leucoencephalopathy (PML), a demyelinating disease caused by the JC virus (JCV), occurs in immunosuppressed patients and carries a poor prognosis. A favourable outcome is reported in two patients with PML and dermatomyositis. Immunosuppressive drugs were stopped in patient 1 but could only be partially tapered in patient 2. The JCV-specific CD8+ T cell response was strong in patient 1 and weak in patient 2. Both were treated with cytosine-arabinoside, and patient 2 was also treated with mirtazapine, a $5HT_{2A}$ receptor antagonist. Combination of these drugs might be helpful to treat HIV-negative patients with PML.

Progressive multifocal leucoencephalopathy (PML) is a severe demyelinating disease of the central nervous system caused by the reactivation of JC virus (JCV) in immunosuppressed patients.[1] Without treatment, only 10% of patients with PML survive more than 1 year. This percentage has risen to 50% in HIV-infected patients with PML who were on highly active antiretroviral treatment. A treatment is deeply needed for HIV-negative patients with PML.

The most frequent causes of immunosuppression leading to PML in HIV-negative patients are leukaemia and lymphoma. Dermatomyositis has infrequently been reported as a cause of PML and when so, the outcome was always fatal.[2–4] We report on two patients with dermatomyositis who developed PML. Immunosuppressive treatment could be stopped in one patient and partially tapered in the other. In addition, both were treated with cytosine-arabinoside (Ara-C), and one of them also with mirtazapine. They had a favourable outcome. These results suggest that in addition to a decrease in the immunosuppressive treatment, these drugs may be helpful to treat HIV-negative patients with PML.

CASE REPORTS

Patient 1

In January 2002, a 52-year-old HIV-negative woman was admitted for progressive psychomotor slowing, word-finding difficulties and dizziness within 1 month of the onset of symptoms. In September 1999, she had been diagnosed with dermatomyositis, on the basis of clinical (dysphagia, proximal symmetric weakness and erythematous lesions of the face, neck and upper chest, increased creatine kinase at 8508 U/l), electrophysiological (reduced motor response, resting potentials, small amplitude and polyphasic potentials) and pathological (moderate inflammation with CD8+ T cells infiltration) criteria.[5]

At the time her neurological symptoms began, she was taking prednisone 15 mg/day and her dermatomyositis was quiescent. The neurological examination showed decreased psychomotor speed, expressive aphasia, moderate short-term memory impairment, left-beating horizontal nystagmus, left peripheral facial palsy and proximal symmetric weakness. Blood testing, including complete blood count, chemistry and microbial serologies, was normal. Brain magnetic resonance imaging (MRI) showed multiple supratentorial non-enhancing white matter lesions; one of them, large, was located in the white matter of the left frontal lobe and extended into the internal capsule (fig 1A). One infratentorial enhancing lesion was found at the root of the left VII and VIII cranial nerves (fig 1B). Two lumbar punctures were performed 8 days apart. The first showed a white cell count at 14/mcl with a lymphomonocytic predominance and 0.64 g/l of proteins; the second one was entirely normal. Polymerase chain reaction (PCR) for JCV was negative in both lumbar punctures. However, PML was strongly suspected, thus a stereotactic biopsy was carried out in the left frontal lobe. Histological examination showed typical features of PML—namely, demyelination areas, enlarged oligodendrocytes with nuclear inclusions, lipid-laden macrophages and bizarre astrocytes. PCR for JCV DNA was positive on this biopsy specimen, establishing the diagnosis of PML.

Prednisone was withdrawn and Ara-C (2 mg/kg/day for 5 days) started, but motor aphasia worsened and there was new onset of dysarthria and right-arm weakness. Another MRI showed an extension of the brain lesions. A second course of 5 days of Ara-C was given 2 weeks after the first one. Then, the patient's condition stabilised and she showed a slow but continuous improvement. Fifty months after onset of PML, she had only mild cognitive impairment and a right hand tremor; a subsequent brain MRI showed a marked decrease of PML lesions (fig 1C).

Four months after the onset of PML, using a 51-Cr release assay, we could determine that she had a strong JCV-specific CD8+ cytotoxic T lymphocyte response against at least two epitopes of VP1, the major capsid protein of JCV.[6]

Patient 2

In July 2004, a 48-year-old HIV-negative man was admitted because of a loss of vision progressing over 6 weeks. Dermatomyosits had been diagnosed 4 years before these events on the basis of progressive generalised fatigue, dysphagia, proximal tetraparesis and rash; increased creatine kinase (2369 U/l) and antinuclear antibody (1/5120); signs of proximal myopathy at the electroneuromyography; and inflammatory myopathy with T cells infiltrate without signs of vasculitis on muscle biopsy.[5]

When his vision troubles started, he was on a combination of prednisone 5 mg/day, mycophenolate mofetil 1.25 g/day, ciclosporin A 275 mg/day, and intravenous immunoglobulins

Abbreviations: Ara-C, cytosine-arabinoside; JCV, JC virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leucoencephalopathy

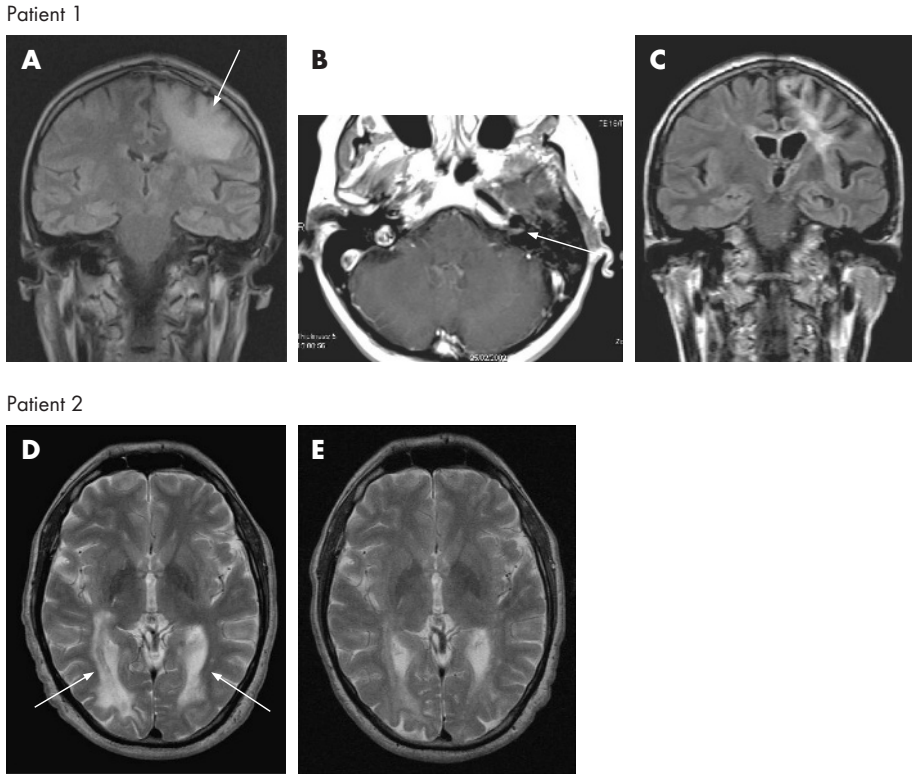

Figure 1 Neuroradiological features of progressive multifocal leucoencephalopathy on brain magnetic resonance imaging. (A) Patient 1: on this coronal slice (fluid-attenuated inversion recovery), there is a large hyperintensity in the left frontal white matter that extends into the internal capsule (arrow). No mass effect or contrast enhancement is present. (B) The left facial (VII) and vestibulocochlar (VIII) bundle enhances after contrast administration on this T1-weighted axial sequence. (C) Compared with (A), 2 years later, the hyperintense lesion has decreased in volume and only subcortical necrosis and atrophy are present. (D) Patient 2: on this T2-weighted axial slice, hyperintense lesions are present along the optic radiations, extending from the thalami to the occipital lobes on both sides (arrows). (E) After treatment, 4 months later, the size and the intensity of these lesions are markedly decreased.

2 g/kg once a month for persistent proximal muscle weakness and dysphagia. The neurological examination showed decreased visual acuity (20/70 on the right and 20/50 on the left), a left homonymous hemianopia, and a right homonymous inferior quadratanopia and a generalised amyotrophy. Microbial serologies were negative. MRI showed disseminated lesions in the white matter of both occipital lobes and in the splenium of the corpus callosus (fig 1D). The cerebrospinal fluid examination was normal except for a strongly positive PCR for JCV DNA (10^4–10^5 copies/ml).

Immunosuppressive treatment was reduced as much as possible: ciclosporin A was discontinued, but mycophenolate mofetil could be decreased only from 2 g to 0.5 g/day; prednisone (5 mg/day) and monthly intravenous immunoglobulins needed to be maintained. The day after the diagnosis of PML was established, he received a 5-day course of intravenous Ara-C (2 mg/kg/day for 5 days) and an ongoing treatment of mirtazapine 30 mg/day. The patient recovered progressively (fig 1E). Nineteen months after the onset of PML, visual acuity was 20/25 in each eye, with a moderate residual left homonymous hemianopia and a minimal right homonymous inferior quadratanopia.

Two months after the beginning of his neurological symptoms, using the tetramer technology, we could show that after 2 weeks of in vitro stimulation, 0.58% of the CD8+ T cells of this patient recognised a human leucocyte antigen-A2-restricted epitope of JCV named $VP1_{p100}$; however, no CD8+ T cells recognised the other JCV VP1 human leucocyte antigen-A2-restricted, $VP1_{p36}$ epitope (technique described in Du Pasquier *et al*[6]). These data show that there was a JCV-specific CD8+ T cell response, albeit of low magnitude.

DISCUSSION

We report on two HIV-negative patients with treated dermatomyositis who developed PML and improved dramatically. This favourable outcome stands in contrast with the few existing reports of patients who developed PML with dermatomyositis as an underlying disease and who invariably had a fatal issue[2–4] (table 1).

Among other neurological deficits, patient 1 presented with a peripheral facial palsy. On brain MRI, there was a contrast enhancement of the bundle of VII and VIII cranial nerves (fig 1B). An extensive search for various pathogens, including human simplex virus-1 and 2 and Lyme disease was negative. We consider that JCV was the cause of this lesion. Indeed, the proximal part of VII and VIII cranial nerves has a central type of myelination and can thus be targeted by pathophysiological mechanisms specifically affecting the central nervous system, such as a plaque in multiple sclerosis.[7] Interestingly, this rare feature of PML has been described in another patient with dermatomyositis and PML[8] (PML outcome in this patient is not reported by the authors).

Patients with PML who are able to develop an inflammatory response have a better outcome than those who cannot. For instance, the improved course of PML in HIV-infected patients who are on highly active antiretroviral treatment is thought to be due to an immune reconstitution, rather than a direct anti-JCV effect.[9] Patient 1 showed two surrogate markers of an inflammatory response against JCV: a contrast enhancement of PML lesions on brain MRI[10] and detection of a strong JCV-specific CD8+ T cell response.[6] It is likely that the cessation of prednisone had a role in this immune

Table 1 Clinical data on the five patients with dermatomyositis who developed progressive multifocal leucoencephalopathy (PML)

	Pre-PML DM duration	Immunosuppressive treatment at and after PML diagnosis	Ancillary examinations	PML onset and course	PML-specific treatment	PML outcome
Patient 1, F, 52 years, HIV negative	5 years	Prednisone 15 mg/day, → stop	MRI: T2-WM lesions. Gd+ cranial nerve roots VII and VIII. CSF: transitory slight pleocytosis, JCV PCR− Biopsy: typical PML lesions, JCV PCR+ JCV−sp CTL: +++	Psychomotor slowing, aphasia, L peripheral facial palsy, nystagmus over 1 month. Then onset of dysarthria, R brachial weakness	2 courses of Ara-C 2 mg/kg/day for 5 days each, 2 weeks apart	Improvement after the second course of Ara-C
Patient 2, M, 44 years, HIV negative	2.5 years	Immunoglobulin 2 g/kg/month → unchanged Mycophenolate mofetil 2g/day → 0.5 g/day. Prednisone 5 mg/day →unchanged Ciclosporin A → stop	MRI: T2-WM lesions, CSF: JCV PCR+ JCV-sp,CTL: +	Visual acuity decrease, L hemianopia and R inferior quadratanopia over 6 weeks	One course of Ara-C 2 mg/kg/day for 5 days, mirtazapine 30 mg/day	Improvement after one course of Ara-C and ongoing treatment of mirtazapine 30 mg/day
Aksamit[2], F 72 years, HIV negative	N/A	Azathioprine → stop	Biopsy: little inflammation, ISH+ for JCV. MRI: Onset of Gd+ WM lesions after Ara-C. Autopsy: marked inflammation; JCV ISH+	Cognitive and personality changes over 2 months	Ara-C 2 mg/kg/day for 5 days	Death in 4 weeks
Gentile *et al*[3], M, 45 years, HIV negative	7 months	Prednisone → stop Immunoglobulins → stop Ciclosporin A → stop	MRI: multiple T2 WM lesions. Autopsy: marked inflammation. Typical PML changes with intranuclear viral bodies	Altered consciousness. Progressive bilateral pyramidal disorder	None	Death in 1 month
Tubridy *et al*[4], F, 43 years, HIV negative	5 years	Prednisolone 10 mg/day → stop	MRI: rapidly progressing T2-WM lesions. CSF: normal. JCV PCR− Biopsy: typical for PML positive JCV antibody	Gait ataxia and dysarthria over 1 month	Cidofovir 5 mg/kg/day. Ara-C 3 pulses 5 mg/kg/ day for 5 days 3 fortnightly pulses of both	Death in 3 months

Ara-C, cytosine-arabinoside; CSF, cerebrospinal fluid; F, female; Gd+, gadolinium enhancement of T1-weighted lesions on brain MRI; ISH, in situ hybridisation; JCV, JC virus; JCV-sp. CTL, cytotoxic T lymphocytes specific for JC virus; L, left; M, male; N/A, not available; PCR, polymerase chain reaction; R, right; T2, T2-weighted lesions on brain MRI; WM, white matter; →, treatment changes as soon as PML was diagnosed.

reconstitution. Nevertheless, a direct anti-JCV effect of Ara-C might have had an additional favourable role, as suggested by the fact that she clearly improved after the second course of Ara-C. A benefit of this drug in patients with PML is supported by in vitro data showing a marked decrease of active JCV replication in a human glial cell line.[11] Moreover, one study reported that 36% of HIV-negative patients with PML could survive >1 year when treated with Ara-C.[2] Nevertheless, we can only speculate about the role of Ara-C. Indeed, such as in patient 1, low-dose prednisone treatment was stopped in Tubridy *et al*'s[4] patient, who also received courses of Ara-C and yet had a fatal outcome. A possible explanation for this difference might stem from the fact that Tubridy's patient did not seem to have an inflammatory form of PML, as suggested by the absence of contrast-enhancing lesions on brain MRI.

Conversely, the JCV-specific immune response of patient 2 was modest. The detection of JCV VP1-specific CD8+ T cells using tetramer staining was weak. This weak immune response is not surprising, considering that he was on major immunosuppressive treatment at the time of PML onset and that, owing to dermatomyositis severity, this treatment could only be decreased but certainly not stopped. Yet his condition improved dramatically. Dermatomyositis of Gentile *et al*'s[3] patient was also treated with high doses of prednisone, immunoglobulins and ciclosporin A when PML occurred. He died despite complete cessation of this treatment.[3] Therefore, additional factors must be looked for to explain the favourable issue of patient 2. As soon as the diagnosis of PML was established, he received a 5-day course of Ara-C and a long-term treatment of mirtazapine, and improved rapidly. The anti-depressant drug mirtazapine is a $5HT_{2A}$ receptor antagonist that efficiently crosses the blood–brain barrier[12] and binds to a substantial amount of $5HT_{2A}$ receptors.[13] It was recently shown that JCV uses the serotoninergic $5HT_{2A}$ cell membrane receptor to infect cells[14] and that drugs binding to these receptors block JCV infection of glial cells in vitro.[15] Thus, this class of drugs might represent a treatment option for patients with PML.[14] Might mirtazapine, together with Ara-C, have helped to contain PML in patient 2?

There is no specific treatment for PML. The most important measure to take in HIV-negative patients with PML is cessation of immunosuppressive drugs. However, this is not always possible and, even when this is done, the prognosis remains poor. Our results suggest that a combined treatment of Ara-C and a $5HT_{2A}$ receptor antagonist, such as mirtazapine, might be of help in treating HIV-negative patients with PML. However, further studies are clearly needed to confirm this observation.

ACKNOWLEDGEMENTS

We thank Lindsey Cameron for her help in editing this manuscript.

Authors' affiliations

S Vulliemoz, F Picard, T Landis, Service de Neurologie, Hôpitaux Universitaires de Genève, Geneva, Switzerland
F Lurati-Ruiz, R A Du Pasquier, Service d' Immunologie et allergologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
F-X Borruat, Unité de Neuro-ophtalmologie, Centre Hospitalier Universitaire Vaudois, Lausanne
J Delavelle, Unité de Neuro-radiologie, Hôpitaux Universitaires de Genève
I J Koralnik, HIV/Neurology Center, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
T Kuntzer, J Bogousslavsky, R A Du Pasquier, Service de Neurologie, Centre Hospitalier Universitaire Vaudois

This work was supported in part by grants from the Swiss National Foundation (FN 3200BO-104262 and PP00B-106716) and from the Swiss Society for Multiple Sclerosis to RADP, and grants R01 NS/AI 041198 and 047029 from the National Institutes of Health, USA to IJK.

Competing interests: None declared.

Informed consent was obtained from the patients described in this report.

Correspondence to: R A Du Pasquier, Service de Neurologie and Service d'Immunologie, Centre Hospitalier Universitaire Vaudois, BT-02 1011 Lausanne, Switzerland; renaud.Du-Pasquier@chuv.ch

Received 27 March 2006
Revised version received 29 May 2006
Accepted 3 June 2006

REFERENCES

1 **Padgett BL**, Walker DL, ZuRhein GM, *et al*. Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. *Lancet* 1971;**1**:1257–60.
2 **Aksamit AJ**. Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside. *J Neurovirol* 2001;**7**:386–90.
3 **Gentile S**, Sacerdote I, Roccatello D, *et al*. Progressive multifocal leukoencephalopathy during cyclosporine treatment. A case report. *Ital J Neurol Sci* 1996;**17**:363–6.
4 **Tubridy N**, Wells C, Lewis D, *et al*. Unsuccessful treatment with cidofovir and cytarabine in progressive multifocal leukoencephalopathy associated with dermatomyositis. *J R Soc Med* 2000;**93**:374–5.
5 **Tanimoto K**, Nakano K, Kano S, *et al*. Classification criteria for polymyositis and dermatomyositis. *J Rheumatol* 1995;**22**:668–74.
6 **Du Pasquier RA**, Kuroda MJ, Schmitz JE, *et al*. Low frequency of cytotoxic T lymphocytes against the novel HLA-A*0201-restricted JC virus epitope VP1(p36) in patients with proven or possible progressive multifocal leukoencephalopathy. *J Virol* 2003;**77**:11918–26.
7 **Bridger MW**, Farkashidy J. The distribution of neuroglia and schwann cells in the 8th nerve of man. *J Laryngol Otol* 1980;**94**:1353–62.
8 **Cuevas L**, Fuchs H. Progressive multifocal leukoencephalopathy and immunosuppression. *Ann Rheum Dis* 2004;**63**:112–13.
9 **Clifford DB**, Yiannoutsos C, Glicksman M, *et al*. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology* 1999;**52**:623–5.
10 **Berger JR**, Levy RM, Flomenhoft D, *et al*. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 1998;**44**:341–9.
11 **Hou J**, Major EO. The efficacy of nucleoside analogs against JC virus multiplication in a persistently infected human fetal brain cell line. *J Neurovirol* 1998;**4**:451–6.
12 **Uhr M**, Grauer MT, Holsboer F. Differential enhancement of antidepressant penetration into the brain in mice with abcb1ab (mdr1ab) P-glycoprotein gene disruption. *Biol Psychiatry* 2003;**54**:840–6.
13 **Bhagwagar Z**, Hinz R, Cunningham VJ, *et al*. Occupancy of the 5-HT2A Receptor by Mirtazapine: a PET study with [11C]MDL 100,907. *J Psychopharmacol* 2003;**17**:A14.
14 **Elphick GF**, Querbes W, Jordan JA, *et al*. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science* 2004;**306**:1380–3.
15 **Baum S**, Ashok A, Gee G, *et al*. Early events in the life cycle of JC virus as potential therapeutic targets for the treatment of progressive multifocal leukoencephalopathy. *J Neurovirol* 2003;**9**(Suppl 1):32–7.